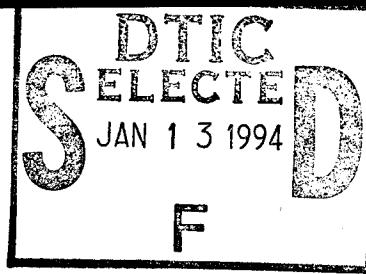


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CHRONIC PHYSIOLOGICAL EFFECTS OF POSITIVE PRESSURE BREATHING IN A HIGH SUSTAINED G ENVIRONMENT

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FINAL REPORT FOR THE PERIOD DECEMBER 1991 - JUNE 1992

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TECHNICAL REVIEW AND APPROVAL

AL/CF-TR-1993-0073

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER



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Preface

Research was performed under WU ILIRBB10 as a FY 90 Innovative Independent Laboratory Research program. Drs. James Cooper and William Albery were co-principal investigators. The research was conducted through the Engineering Services Contract number F-33615-89-C-0574 by Systems Research Laboratories. The authors wish to thank Susan Young from the Armstrong Laboratory Vivarium, Mr. Alva Karl, Melissa Frey, and Beverly Girten from Systems Research Laboratories; Lt. Col John Latendresse from the Army Medical Research Unit, Toxicology Division; Mr. Chuck Goodyear and Deepa Naishadham from Logicon Technical Services Inc who provided statistical analysis support, and a special thanks to Miss Grady Ripley of Krug International who tailored the G suits used in this study; Bill Collins of the Research Engineering and Fabrication Office, Brooks AFB, TX who hand molded the PPB snout mask; Dr. John Burns of the School of Armstrong Laboratory, Brooks AFB, TX; Dr. John Bonigura from the Ohio State University School of Veterinarian Medicine, who performed and analyzed the two-dimensional echocardiograms; the Dynamic Environment Simulator operation crew; and Mrs. Tamara Chelette of the Combined Stress Branch, Armstrong Laboratory who helped in organizing this study.

The animals used in this study were handled in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals, prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, DHHS, National Institute of Health Publication #85-23, 1985, and the Animal Welfare Act of 1966, as amended.

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ABBREVIATIONS USED

LA-2D - Left atrial dimension using two-dimensional imaging

Aorta - aortic dimension

RR - ECG R wave to R wave time interval

LVWd - Left ventricular wall dimension

LVIDd - Left ventricular interior diameter at end-diastole

IVSd - Interventricular septum dimension

RVIDd - Right ventricular interior diameter at diastole

LVWs - Left ventricular wall dimension at end-systole

LVIDs - Left ventricular interior diameter at end-systole

IVSs - interventricular septum dimension at end-systole

IVSamp - Excursion of the ventricular septum in systole

IVScv - Intraventricular septum curvature

RVWd - Right ventricular wall dimension

RA2D - Right atrium two dimensional echocardiogram

PA - Pulmonary artery dimension

PA_vel - Pulmonary artery velocity

TV_E_vel - Tricuspid valve end-flow velocity

TV_A_vel - Tricuspid valve arterial contraction velocity

P1_vel - Pulmonary insufficiency velocity

RA/LA - Right atrium/left atrium ratio

RVw/LVw - Right ventricular wall/Left ventricular wall ratio

RVid/LVid - Right ventricular interior/Left ventricular interior dimension ratio

PA/AO - Pulmonary artery dimension/Aortic dimension ratio

LV_SF % - Left ventricular shortening fraction % change from baseline

ATAGS - Advanced technology anti-G suit

PPB - Positive Pressure Breathing

mm Hg - Millimeters of mercury

B.W. - Body weight

Vent - Ventricle

kg - Kilogram

gm - Gram

mg - Milligram

Hz - Hertz

psi - Pounds per square inch

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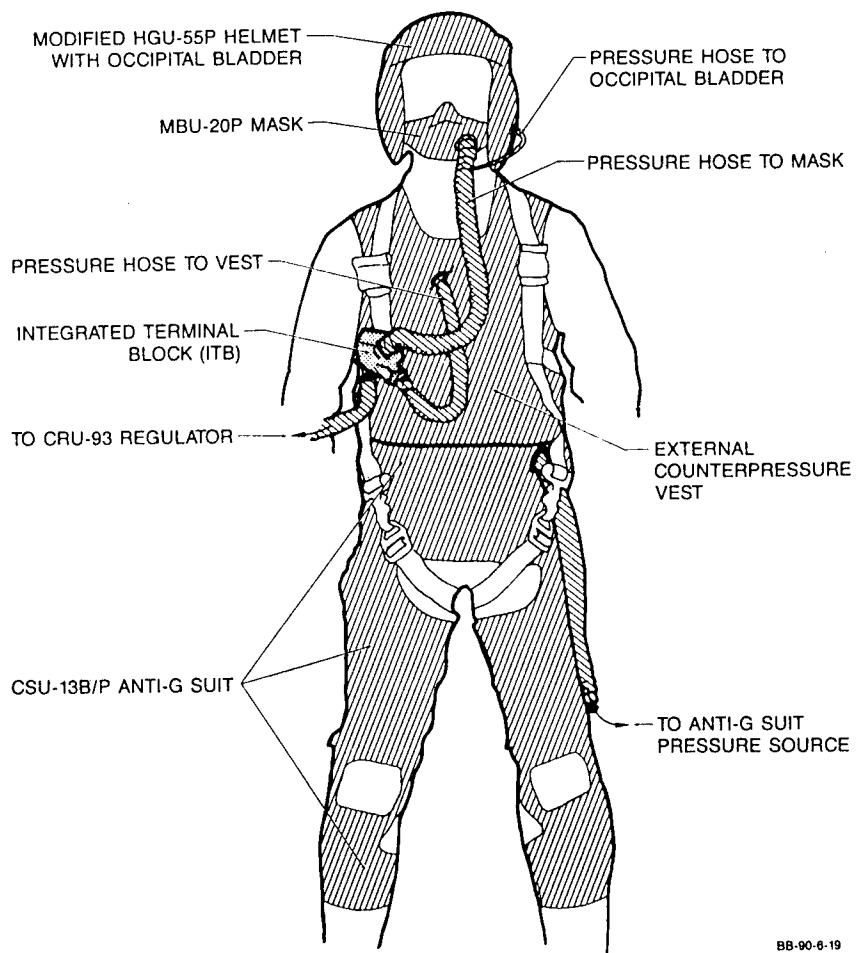
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INTRODUCTION

A new positive pressure breathing system for G-protection known as COMBAT EDGE is currently being evaluated for use in both the USAF and NAVY F-16 and the USAF F-15 aircraft. This system is being used in conjunction with the current Air Force standard CSU-13 B/P anti-G suit or the new Advanced Technology Anti-G Suit (ATAGS) being developed by the Armstrong Laboratory. The COMBAT EDGE system is comprised of a low profile oxygen mask (MBU-20P), a HGU-55P helmet modified with an occipital bladder used as a tensioning device for the mask, a counterpressure vest, and an integrated terminal block which connects both the oxygen mask and the counterpressure vest to the breathing regulator (Figure 1). COMBAT EDGE has been shown to enhance a pilots endurance to sustained acceleration.

Figure 1
COMBAT EDGE G PROTECTION SYSTEM



If this system is fully deployed, pilots can be safely exposed to a high time duration dose of positive pressure breathing over the course of a 20 year flying career. Recent concerns in this area raised by the Aerospace Medical Community have dealt primarily with the possibility of physiological effects of long duration exposure to PPB manifesting themselves into occupational health risks. To be more precise, these questions have centered around possible cardiopulmonary physiological effects of PPB.

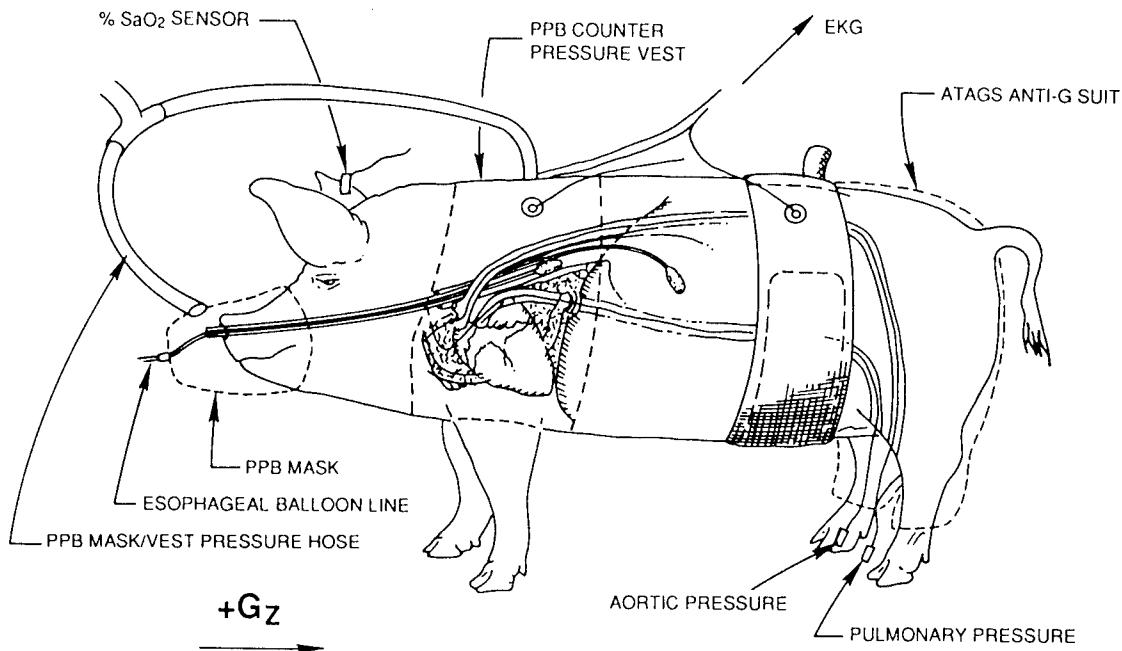
From a historical perspective, PPB has been used extensively by both the Royal Air Force in Britain and by the United States Air Force over the past 40 years to protect pilots from the physiological effects of altitude. Ackles (1) described the use of PPB by Britain's Royal Air Force for high altitude protection. It is important to point out that the levels of PPB used for altitude protection are lower (30 mm Hg maximum), than those proposed for G-protection (60 mm Hg maximum).

To address the question of potential occupational health risk effects from PPB, the Armstrong Laboratory has conducted two separate experiments to investigate both short and chronic exposure to PPB. In 1991, Burns et al. (2) reported the results of a study conducted at Brooks AFB, TX which investigated the effects of short duration exposure to PPB using the swine as the experimental test animal. Results from this study showed no significant physiologic findings. This report describes the follow-on PPB study conducted at the Armstrong Laboratory, Wright-Patterson AFB, OH, which examined chronic exposure to PPB. Swine were, again, used in order to enable researchers to compare results of the two studies. The miniature swine was selected as the human analog in this study because the animal's cardiopulmonary vasculature is very similar to that of a human. In addition, the swine will perform a natural, rhythmic straining maneuver under G, much like a human who is trained to strain during exposure to G. Previous work has shown the swine to be an excellent analog of the human in studying the effects of high, sustained G (2, 3).

METHODS

Eight male unanesthetized Minihanford miniature swine were selected for the study. Four served as experimental test animals and four served as control animals. Ages ranged from 6 to 7 months. Of the four control animals, three were euthanized at age 12 months and the one remaining control served as a live control and was euthanized along with the experimental test animals. The four control animals also acted as controls for a second unrelated experiment which explains the differences in age between the test and control animals. Experimental test animals were exposed to high G on 27 separate test days.

Echocardiograms were performed on all of the experimental test animals pre and post experiment. Post experimental echocardiograms were performed on the one live control only.



Instrumentation: Figure 2
ANIMAL INSTRUMENTATION

Instrumentation: Blood pressure recording catheters were surgically positioned in each of the four test animals prior to and following the 90 day test period (test days 1 and 27). General surgical anesthesia for the procedure was provided using a mixture of Isoflorthane and nitrous oxide. Prior to the initial G exposure test day 1, a 2 French Milar catheter and 7 French Swan-Ganz catheter were introduced into the animal's vascular system through an incision in the right femoral vein (Figure 2). The catheters were advanced anteriorly through the animal's right heart and into the pulmonary artery. Similarly, a 5 French Milar catheter was inserted into the femoral artery of the same limb and the tip advanced into the area of the aortic arch. Final placement of both catheters was accomplished under fluoroscopy. Prior to the final G exposure, test day 27, the above catheterization procedures were repeated. Vascular access in this instance being gained through vessels in the animal's left and right rear limbs. The distal ends of both Milar catheters were attached to Milar TC-510 control units (Model SPC-3505-F). The Swan-Ganz catheter was connected to an American Edwards Laboratories

Cardiac Output computer (Model COM-1-RS). Both of these units were mounted on the animal platform of the centrifuge. Also mounted on this platform was a remotely activated infusion syringe capable of injecting iced saline through the thermal dilution port of the Swan-Ganz catheter. This experimental preparation allowed investigators to simultaneously record pulmonary artery pressure, aortic artery pressure, and cardiac output at various G levels while the animals were exposed to positive pressure breathing.

In addition to the above invasive procedures, pre and post experimental echocardiograms were obtained on each of the test animals. The pigs were anesthetized with Ketamine HCL (20 mg/kg) during these procedures. An Irex echocardiograph was used to obtain the recordings.

During each of the 27 centrifuge procedures, Baxter pre-gelled ECG electrodes attached to each side of the thorax and one attached to the lumbar area of the animal's back, enabled the continuous recording of the heart rate and electrocardiographic activity. An OMEGA 0-5 PSIG pressure transducer (model PX143-05 BG 5V) connected to the oxygen mask was used to record inspiratory and expiratory pressures as well as respiratory rate. A similar OMEGA 0-15 PSIG transducer (model PX142-015 G 5V) monitored anti-G suit pressure.

G-Protective Equipment: Human exposure to PPB was simulated in the pig by fitting each animal with a custom made PPB mask, counterpressure vest, and a full coverage anti-G suit similar in design to the prototype ATAGS (Figure 3.). Preliminary studies employing this equipment revealed that full coverage ATAGS induced severe respiratory difficulty in the subject animals when inflated to maximum pressure. This problem was solved by assuring that the ATAGS did not extend over the animal's ribs and by limiting the G suit pressure to 6 psi rather than 10 to 11 psi. Different pneumatic pressures in the mask and counter pressure vest versus that in the ATAGS were obtained using a tandem G-valve setup. One Alar valve was set at a 90 degree angle to the G vector which provided a maximum of 11 psi to the Tactical Life Support breathing regulator (Garrett Corporation serial number 31307-1) and the counterpressure vest. A second Alar G-valve was offset 45 degrees from the G vector thus assuring a maximum of 6 psi ATAGS pressure. This G-valve arrangement provided 55-60 mm Hg positive pressure to the mask.

Once instrumented and fitted with a mask and suit, the fully conscious pig was placed on the animal platform of the centrifuge (Figure 4). This device, also known as the Dynamic Environment Simulator, is used for both animal and human acceleration research. The animal platform is 20.5 feet from the center of rotation.

G-Profiles: Acceleration exposures consisted of a 10 minute 5 to 9 +Gz simulated aerial combat maneuver with 10 second plateaus at both +5 and +9 Gz. A 0.5G/second onset rate was used for all G exposures. G vectors and position of the animals during acceleration are illustrated in Figure 5.

Necropsy Procedures: Three of the four swine (#621 622 and 623), acted as controls for two separate experiments; this resulted in the animals being euthanized 5 months prior to the

completion of this study. Hearts and lungs were immersed in buffered formalin and retained for measuring gross perimeters and histopathologic examination after the four experimental animals and one live control were euthanized.



Figure 3
ANIMAL WEARING THE PPB G-SUIT ENSEMBLE

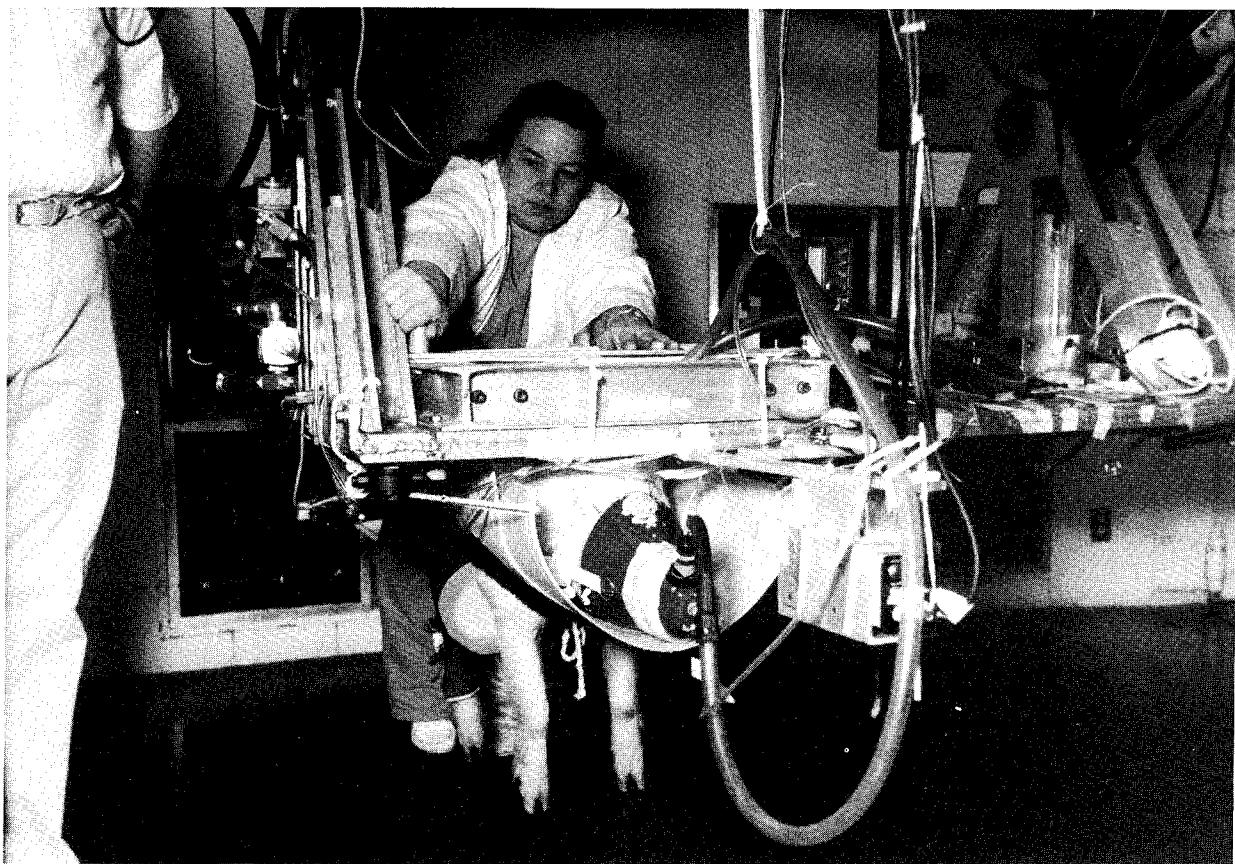
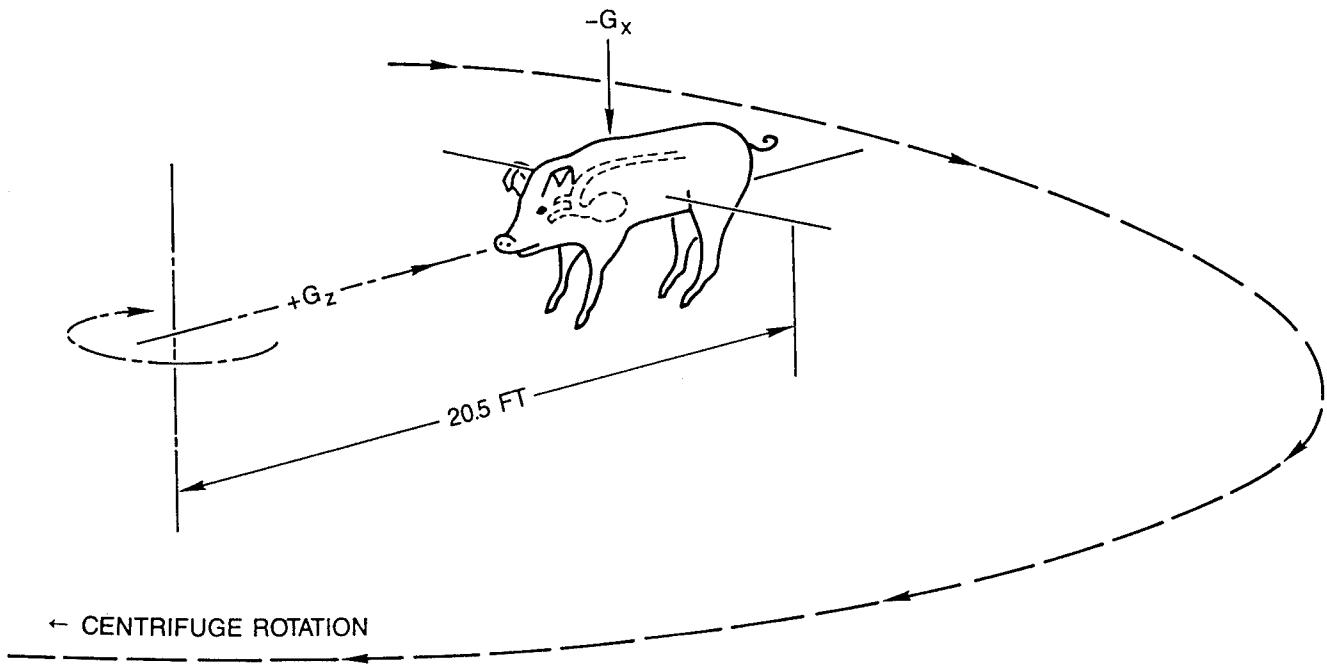


Figure 4
CENTRIFUGE ANIMAL PLATFORM



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Figure 5
ANIMAL POSITION AND G VECTORS

The five remaining swine were anesthetized with ketamine hydrochloride, maintained in a surgical plane of anesthesia with sodium penobarbital as needed, and were perfused with 1% glutaraldehyde and 4% formaldehyde mixture 4CF-1G, McDowell, 1976 (3), via the abdominal aorta. The lungs were also perfused via the trachea with buffered formalin. The hearts and lungs were retained in 4CF-1G. Additional tissue (see gross examination) were retained in buffered formalin. The hearts from these 5 pigs were weighed, trimmed, and dissected into individual chambers and reweighed 48 hours after necropsy. The three other control hearts were similarly prepared. All tissues were paraffin embedded, sectioned at 3 microns, and stained with hematoxylin and eosin for routine histopathologic examination.

Data Collection: Mask pressure, heart rate, aortic pressure, pulmonary artery pressure, and respiration were sampled at a rate of 100 Hz and stored on computer disk. In addition, real time stripchart recordings were made of the G-level, EKG, aortic pressure, pulmonary artery pressure, mask pressure, respiration and percent arterial oxygen saturation. Cardiac output

data were manually recorded from the cardiac output device via a video picture of the cardiac output monitor's LED read out which was provided by a remote camera mounted on the animal platform of the centrifuge.

Statistical Analysis: Paired T-tests were used to compare data collected on day one versus day 27 of the experimental period.

RESULTS

Of all the parameters monitored, only mean aortic pressure recorded on day 27 at +9 Gz differed significantly from day 1 baseline levels ($p < 0.05$). Although not statistically significant, of interest is the fact that pulmonary artery pressure in three of the animals tested reached 120 mm Hg during the +9 G acceleration. Missing pulmonary artery pressure data for animal 152-5 was caused by the loss of arterial patency. In addition, day 1 data collection on animals 159-5 and 159-6 stopped abruptly due to the animals experiencing gravity induced loss of consciousness (Figure 6). Other data collected and analyzed are shown in the following figures: respiratory rate (Figure 7), cardiac output (collected only during +9 G peaks; equipment failure was responsible for not obtaining day 1 cardiac output data on animal 159-5, Figure 8), heart rate (Figure 9), and aortic pressures (Figure 10). Data along the x-axis in Figures 6 through 10 illustrate the various physiological data collected at both +5 and +9 Gz. This axis also depicts the various physiological parameters for each of the sixteen +9 Gz plateaus. The +5 to +9 G SACM lasted for 10 minutes in duration.

Echocardiographic Analysis: Of the 25 different echocardiographic measurements taken on each animal, no abnormal physiologic or morphologic changes were observed. There was, however, an increase in pulmonary artery velocity in all experimental animals. Mean pulmonary artery velocities for day 1 were 72.25 cm/sec, compared to day 27 with mean pulmonary velocities of 117.00 cm/sec. The 44.75 cm/sec change observed in these values does not exceed the upper limits of normal for these animals (Bonaguri, 1992) (see Appendix A). Although pulmonary artery blood flows appear to be elevated in comparison to the pre-baseline values, these values are within normal limits for the pulmonary artery. Echocardiographic data are graphically illustrated in Appendix B.

Gross Examination: Gross necropsies were conducted on each animal. Histologic examinations were performed on the following tissue: lungs, heart, liver, gallbladder, kidneys, adrenals, brain, and eyes of both the control and experimental animals. All animals were reported to be in excellent physical and nutritional condition prior to necropsy. Gross examination findings did reveal an increase in the mass of the left atrium in all test animals (Table 1 and 2).

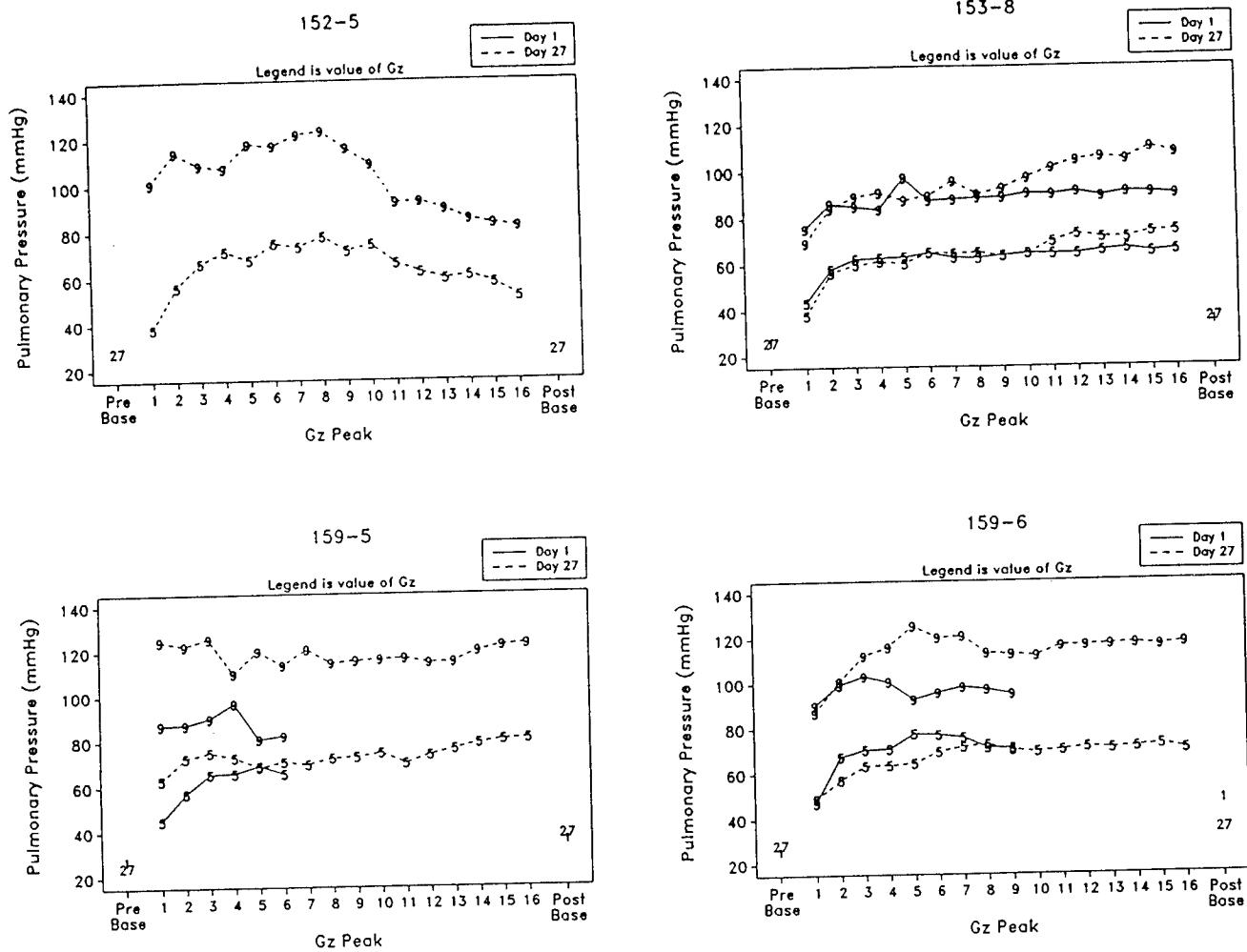
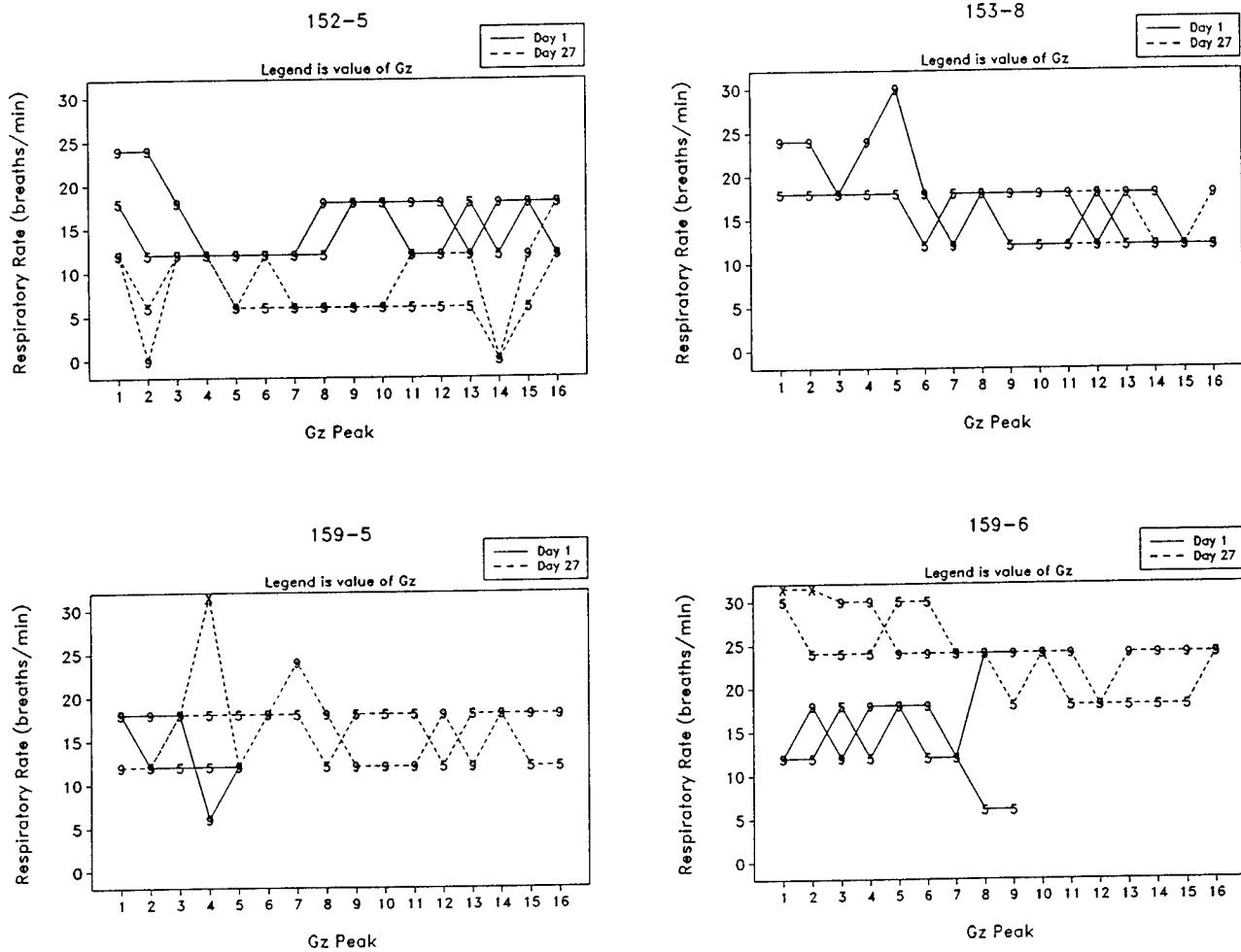


Figure 6
PULMONARY ARTERY PRESSURE
(N=4)



X indicates Rate > 32

Figure 7
RESPIRATORY RATE
(N=4)

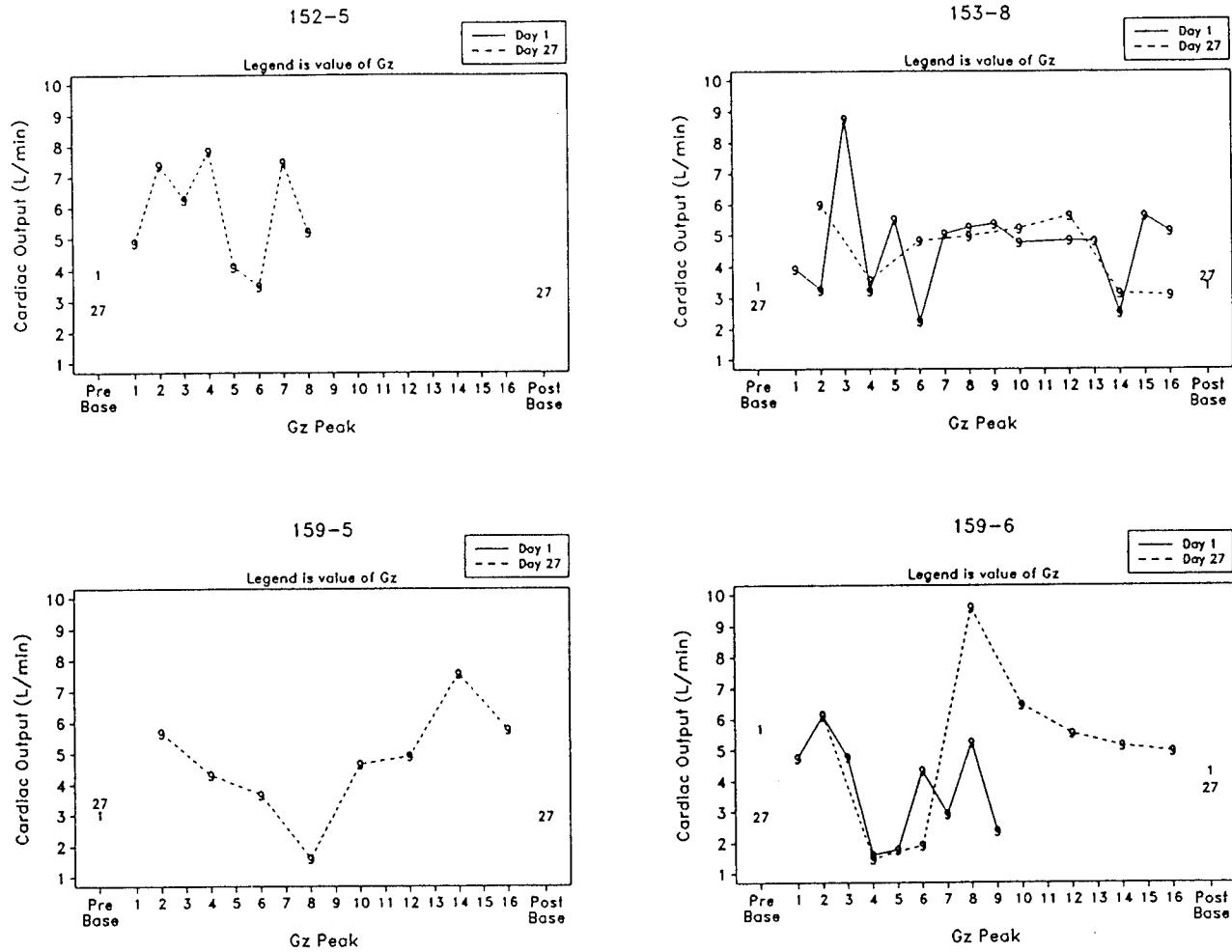


Figure 8
CARDIAC OUTPUT
(N=4)

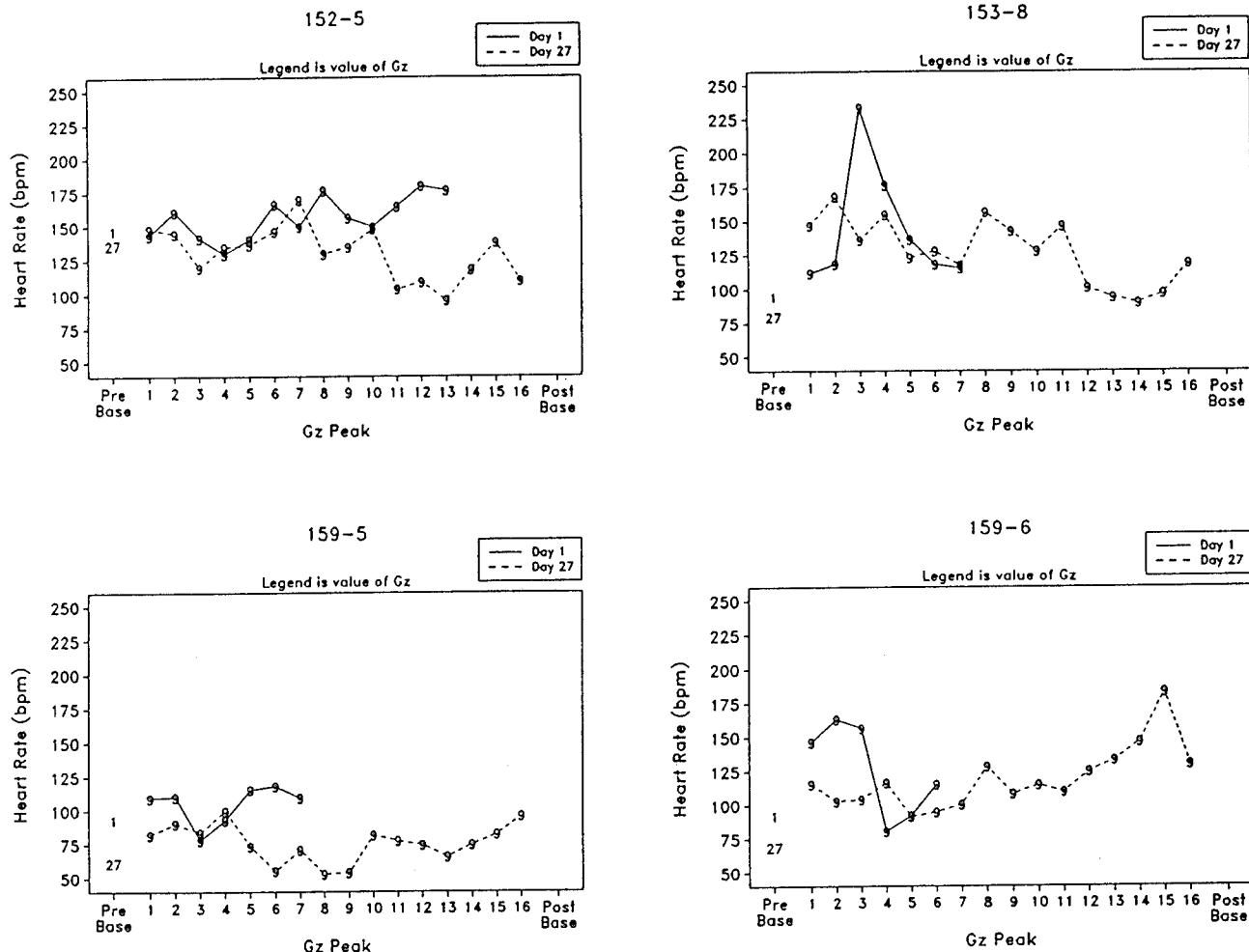


Figure 9
HEART RATE
(N=4)

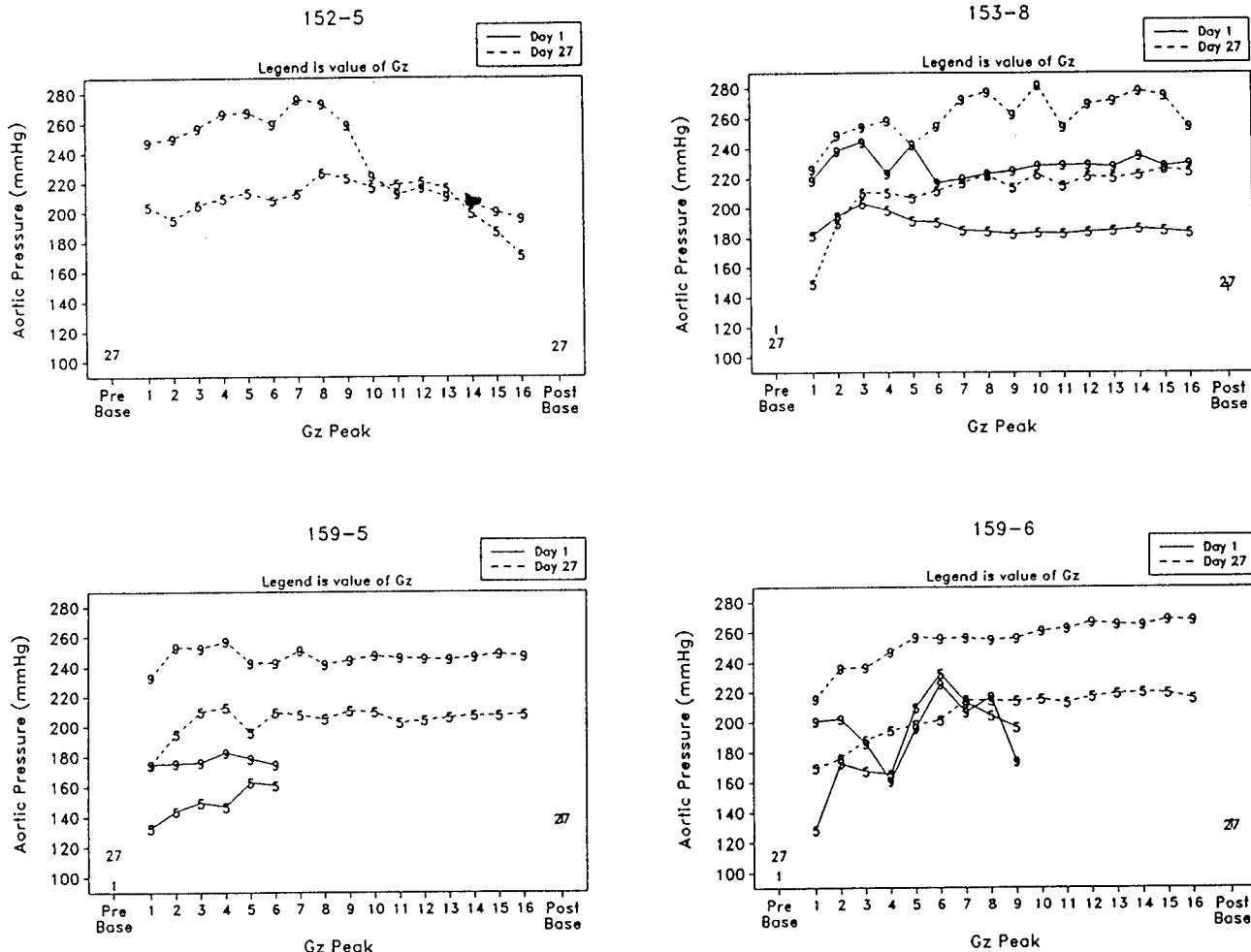


Figure 10
AORTIC
PRESSURE
(N=4)

Table 1
GROSS EXAMINATION OF TEST ANIMAL HEARTS

PIG NUMBER	450	451	452	453
BODY WT (Kg)	45.4	38.6	33.0	40.0
HEART FIXED (gm)	177.8	154.6	126.9	184.1
HEART TRIMMED (gm)				
LT ATRIUM	11.1	12.3	11.4	9.7
RT ATRIUM	12.9	10.5	9.8	11.2
LT VENT & SEP	107.5	94.0	79.8	110.1
RT VENT	34.6	27.7	21.8	43.0
TOTAL WT	166.1	144.5	122.8	174.0
MASS RATIOS				
HEART/BODY WT	0.37	0.37	0.37	0.43
RT VENT/HEART	0.21	0.19	0.18	0.25

Table 2
GROSS EXAMINATION OF CONTROL ANIMAL HEARTS

PIG NUMBER	44-8	48-6	65-4	65-7
BODY WT (Kg)	44.6	33.8	38.0	34.4
HEART FIXED (gm)	199.8	134.0	164.4	149.2
HEART TRIMMED (gm)				
LT ATRIUM	9.2	5.8	7.0	8.6
RT ATRIUM	12.2	8.1	8.5	8.6
LT VENT & SEP	129.4	79.9	100.2	83.6
RT VENT	36.3	28.5	29.5	31.6
MASS RATIOS				
HEART/BODY WT	0.42	0.36	0.38	0.38
RT VENT/HEART	0.19	0.23	0.20	0.24

Histopathologic Examination: Tissue samples of control animals were obtained from the lungs, heart, aorta, and the pulmonary trunk. Heart mass, heart to body mass ratio, and right ventricle to heart ratio data for all animals are shown in Appendix B. Two of the four experimental animals showed a mild degree of fibrosis in the lung while none of the control animals including the live control showed any degree of lung fibrosis. All other tissue taken from other organs were essentially normal. Neither gross nor histopathological examination of the left atrial myocardium or mitral valve accounted for the increase in left atrial weight. The pathological findings are summarized in Appendix C.

DISCUSSION

The main objective of this study was to examine the cardiopulmonary effects of PPB following a simulated life time dose of PPB with high G for a typical Tactical Air Force fighter pilot. In recent years, the Aerospace Medical Community has voiced concerns pertaining to the longitudinal physiological effects of repeated exposure to PPB. One of the major concerns is that repeated exposure to high Gz will cause acute RV dilatation resulting in chronic dilatation and RV pathology. To better understand the effects of chronic exposure to maximum levels of PPB, this study was designed to apply the maximum level of PPB provided by current COMBAT EDGE regulators (60 mm Hg) at a G dose which would exceed that encountered in typical fighter pilot's career. As a result, each animal received over 400 -10 sec exposures to 60 mm Hg at +9 Gz. This equates to a total time of 66 minutes PPB/G dose exposure per animal. Echocardiographic and histopathological examination of the heart revealed no significant change in RV size or changes in tissue morphology. Human testing of COMBAT EDGE has resulted in some human exposures of over 10 minutes of the +5 to +9 G SACM on the Armstrong centrifuge at Brooks AFB, TX.

The chronic exposure of swine to positive pressure breathing or PPB has not presented any severe physiological consequences, however, there are some interesting observations in the area of aortic and pulmonary pressure tracings. There is a statistically significant difference in aortic pressures measured at +9 Gz on day 27 when compared to day 1 ($p < 0.0055$). Differences were also seen for the pulmonary pressures as well, however, these differences were not statistically significant. One explanation for these increases may be attributed to increased peripheral vascular resistance and vascular tone at day 27. The maximum aortic and pulmonary pressures from day 27 did not differ or exceed the maximum aortic and pulmonary pressures reported by Burns et al., 1991 (2). The use of extended coverage or ATAGS like anti-G suit in combination with PPB, has a profound effect on blood pressure in swine. This study showed dramatic increases in aortic peak pressure of 281 mm Hg (measured at the aortic arch) and peak pulmonary pressure of 125 mm Hg (measured in the pulmonary artery). These types of increases in cardiac blood pressures have also been reported in a study using miniature swine (2). Their findings showed that the combination of an extended coverage anti-G suit used in conjunction with PPB during exposures to +9 Gz produced peak left ventricular pressures of 352 mm Hg, peak right ventricular pressures of 163 mm Hg, mean arterial

systolic pressures of 305 mm Hg and mean diastolic pressures of 209 mm Hg.

Another interesting finding from this study was the increase in weight of the left atrium in the experimental test animals. This change occurred in spite of the fact that the histopathological examination of the tissue was essentially normal, and the echocardiographic measurements of the left atrium did not show a significant change in size to account for the weight increase. It is speculated that a larger N size may have brought left atrium weights within normal range. Mass ratios which compared heart to body weight and right ventricle to heart weight showed no significant difference when the mass ratios of the controls were compared to the mass ratios of the test animal population. Histopathological examination of the pulmonary trunk and aorta of both the control and test swine revealed circumferential, and multifocal dense fibrosis. These areas of fibrosis occurred at or near the pulmonic valve and were believed to be normal morphologic findings. In previous work by MacKenzie et al., 1976, (6), and Burton et al., 1976, (7), abnormal myocardial pathology in miniature swine exposed to sustained +Gz levels as high as +15 Gz. Gross and histopathologic examination of the test animal hearts found myofibrillar degeneration, lesions, cardiomyopathy, and subendocardial hemorrhage which were thought to be related to animal heart rates in excess of 200 bpm and an increase in the serum catecholamine levels. These same histopathologic changes were not seen in the current study. One reason for this may be related to the lower heart rates of animals used in this study. As Figure 9 shows heart rates in animals chronically exposed to +9 Gz remained below 200 bpm, with the exception of animal number 153-8 whose heart rate spiked above 225 bpm on the third +9 Gz plateau during day 1 of testing.

CONCLUSIONS

With the exception of increased aortic pressure, the results of chronic exposure to the maximum levels of PPB showed no dramatic effect on the function of the heart or changes in morphology such as hypertrophy of its chambers. In addition, there were no significant histopathologic changes observed upon microscopic examination of various tissues. There were however, increases in left atrial weight noted during gross examination of the heart however, this finding was not substantiated by echocardiographic or morphological changes in atrial tissue thickness. Additional insight into these data would require a more robust study using a larger animal population.

Long term medical tracking of F-16 pilots currently using COMBAT EDGE operationally has already been initiated. To date, there have been no reported aeromedical problems associated with the deployment of COMBAT EDGE. As those pilots who are protected with COMBAT EDGE are medically monitored throughout their careers, it is hoped that this research on an animal model of the human will contribute to a better understanding of the chronic effects of PPB and high G.

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Echocardiographic Data In Numeric Format APPENDIX A

Pig#	Period	Pig#	Period	LA _{2D}	Aorta	RR _s	LWd	LVIDd	IVSD	RVIDd	LWd	IVSs	IVSamp	IVScv	RWd	RA2D	PA	PA _{vel}	TV _E _{vel}	TV _A _{vel}	TR _{vel}	PA _{vel}	RA/LA	RW/LW	RVID/LVID	PA/Ao	LV SF %
65-7CTL	Baseline	65-7CTL	Baseline	3.25	1.95	0.85	0.56	3.95	0.68	1.57	1.18	2.58	1.06	0.66	Normal	0.23	3.19	1.51	66.30	49.30	35.30	neg	0.98	0.41	0.40	0.81	32.97
159-6	Baseline	159-6	Baseline	3.78	2.19	0.61	0.56	3.67	0.79	1.16	1.51	1.81	1.37	1.04	Normal	0.35	2.48	1.69	77.00	79.30	33.30	neg	0.66	0.52	0.32	0.77	31.77
159-5	Baseline	159-5	Baseline	3.33	1.87	1.15	0.48	3.92	0.74	0.64	1.05	2.69	1.18	0.31	Normal	0.24	2.72	1.53	55.60	67.00	41.70	neg	0.82	0.50	0.16	0.82	32.34
153-8	Baseline	153-8	Baseline	3.14	2.37	0.82	0.49	3.28	0.80	1.10	0.97	2.29	1.07	0.42	Normal	0.23	2.58	1.78	90.70	61.70	42.70	alias	0.82	0.47	0.34	0.74	25.82
152-5	Baseline	152-5	Baseline	3.81	2.26	0.62	0.54	3.96	0.80	0.76	0.95	3.03	1.16	0.37	Normal	0.34	2.94	1.85	65.70	58.30	34.00	neg	0.77	0.63	0.19	0.82	31.95
65-4CTL	Baseline	65-4CTL	Baseline	4.43	2.52	0.87	0.59	4.25	0.91	1.48	1.09	2.85	1.11	0.39	Normal	0.33	2.81	1.83	72.30	61.00	40.30	neg	0.83	0.58	0.35	0.73	35.79
48-6CTL	Baseline	48-6CTL	Baseline	3.66	2.16	0.97	0.58	4.27	0.87	1.26	0.71	3.31	0.85	0.31	Normal	0.23	3.28	1.84	88.70	77.70	34.00	neg	1.12 msec	0.90	0.40	0.30	0.84
152-5	Post	152-5	Post	4.28	2.67	1.09	0.59	5.79	1.15	1.68	1.36	4.43	1.43	0.54	Normal	0.35	2.84	1.81	125.00	98.00	55.30	neg	1.29 msec	0.69	0.39	0.29	0.68
153-8	Post	153-8	Post	3.01	2.75	0.5	0.61	3.35	0.81	1.10	1.37	1.95	1.27	0.68	Normal	0.32	2.27	1.37	144.30	62.00	36.00	2.44 msec	0.75	0.52	0.33	0.50	27.68
159-5	Post	159-5	Post	4.19	2.31	0.71	0.53	3.91	1.03	0.92	1.01	2.78	1.31	0.42	Normal	0.30	3.09	1.48	78.00	ND	ND	neg	0.74	0.57	0.24	0.64	31.99
13-7	Post	13-7	Post	4.17	3.07	0.66	0.65	4.21	0.86	1.57	1.19	3.19	1.23	0.53	Normal	0.33	2.93	1.82	59.70	34.70	38.70	neg	0.70	0.50	0.37	0.63	34.52
159-6	Post	159-6	Post	3.45	2.47	0.76	0.65	4.46	0.79	1.20	1.33	2.62	1.31	0.80	Normal	0.38	3.19	1.77	120.70	115.70	82.30	alias	0.92	0.58	0.27	0.72	38.73
Mean	Base(n=7)	Mean	Base(n=7)	3.63	2.18	0.85	0.54	3.90	0.77	1.14	1.07	2.65	1.11	0.50	Normal	0.28	2.85	1.72	70.90	64.90	37.33	-----	0.79	0.51	0.29	0.79	32.23
Mean	Post(n=5)	Mean	Post(n=5)	3.82	2.65	0.74	0.67	4.34	0.93	1.29	1.25	2.99	1.31	0.59	Normal	0.34	2.86	1.87	105.54	62.08	42.46	-----	0.75	0.50	0.30	0.53	36.63

Histopathology Reports APPENDIX B.

PATHOLOGY CLINICAL RECORD					ACCESSION NO. 448-92	
T.D.NO. 005	ANIMAL NO. 13-7	DATE DIED NA	DEPT. THV	SEX M	DISP. A	CONDITION G
SPECIES PIG	STRAIN NA	SOURCE NEC. NO. NA		ORIGIN AF		INVESTGATOR COOPER
AGENT NA	CONCENTRATION NA		EUTHANASIA PENTABARB		NEC. DATE 17MAR92	TIME DIED NA
GENERAL CONDITION GOOD, FAIR, POOR, THIN, EMAC., OTHER,				X FOR TISSUE TAKEN		X FOR EXAM MICRO.

GROSS EXAMINATION

This pig is in excellent physical and nutritional condition. The only observed lesion is multifocal minimal subendocardial hemorrhage; this lesion is believed to be attributed to perfusion. Animal weights and organ weights and measurements are on a separate attached sheet. Organ weights were rounded to the nearest tenth of a gram.

HISTOPATHOLOGIC EXAMINATION

Diffusely within the right ventricle in the section nearest the valve there is prominent subendocardial fibrous thickening with fibrosis extending into the underlying myocardium. This thickening is more pronounced than in any treatment animal with the exception of pig 451.

Focally within the trachea and rarely surrounding the pulmonary airways are small aggregates of lymphocytes.

Gary B. Marit
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Army/Medical Research Unit
Toxicology Division

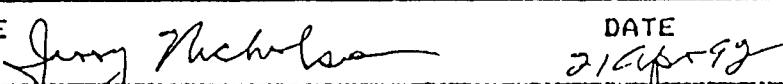
3 April 1992

NASAL SECTION
BONE
BONE MARROW
TRACHEA
LARYNX
ESOPHAGUS
THYROID
PARATHYROIDS
X LUNGS
X HEART
X LIVER
X GALLBLADDER
X SPLEEN
THYMUS
MAND. LYMPH ND.
MEST. LYMPH ND.
X KIDNEYS
X ADRENALS
SALIVARY GLAND
URIN. BLADDER
STOMACH
DUODENUM
PANCREAS
JEJUNUM
ILEUM
COLON
ANUS
TESTES/OVARIES
SEM. VES./UTERUS
PROSTATE/VAGINA
SKIN
MUSCLE
NERVE
MAMMARY GLAND
PITUITARY
BRAIN
X BRAIN
X EYES

PRO. GM/PP/JN	GM TRIM <i>SLW</i>	EMB <i>SLW</i>	R.O.	H.T. SLW
SIGNATURE <i>Gerry Nichols</i>		DATE 27 Mar 92		

PATHOLOGY CLINICAL RECORD					ACCESSION NO. 621-92	
T.D.NO. 005	ANIMAL NO. 48-6	DATE DIED 10/31/91	DEPT. VS	SEX M	DISP. A	CONDITION G
SPECIES SWINE	STRAIN HAN.	SOURCE NEC. NO. NA	ORIGIN OEVM		INVESTGATOR DR. COOPER	
AGENT NA	CONCENTRATION CONTROL		EUTHANASIA ?		NEC. DATE 10/3/91	TIME DIED NA
GENERAL CONDITION GOOD, FAIR, POOR, THIN, EMAC., OTHER,				X FOR TISSUE TAKEN		X FOR EXAM MICRO.
CONTROL ANIMAL ON PPB STUDY				NASAL SECTION BONE BONE MARROW TRACHEA LARYNX ESOPHAGUS THYROID PARATHYROIDS X LUNGS X HEART LIVER GALLBLADDER SPLEEN THYMUS MAND. LYMPH ND. NEST. LYMPH ND. KIDNEYS ADRENALS SALIVARY GLAND URIN. BLADDER STOMACH DUODENUM PANCREAS JEJUNUM ILEUM COLON ANUS TESTES/OVARIES SEM. VES./UTERUS PROSTATE/VAGINA SKIN MUSCLE NERVE MAMMARY GLAND PITUITARY BRAIN X AORTA X PULMONARY TRACT		
 GARY B. MARIT, MAJ, VC, USA Army Medical Research Unit Toxicology Division 30 April 1992						
PRO. DR. M	TRIM M	EMB APP	R.O.	H.T. SLW		
SIGNATURE <i>Jerry Nicholson</i>			DATE <i>31 APR 92</i>			

PATHOLOGY CLINICAL RECORD					ACCESSION NO. 623-92	
T.D.NO. 005	ANIMAL NO. 65-7	DATE DIED 10/31/91	DEPT. VS	SEX M	DISP. A	CONDITION G
SPECIES SWINE	STRAIN HAN.	SOURCE NEC. NO. NA		ORIGIN OEVM		INVESTGATOR DR. COOPER
AGENT NA	CONCENTRATION CONTROL		EUTHANASIA ?		NEC. DATE 10/31/91	TIME DIED NA
GENERAL CONDITION GOOD, FAIR, POOR, THIN, EMAC., OTHER,					X FOR TISSUE TAKEN	X FOR EXAM MICRO.
CONTROL ANIMAL ON PPB STUDY					NASAL SECTION BONE BONE MARROW TRACHEA LARYNX ESOPHAGUS THYROID PARATHYROIDS <input checked="" type="checkbox"/> LUNGS <input checked="" type="checkbox"/> HEART <input checked="" type="checkbox"/> LIVER GALLBLADDER SPLEEN THYMUS MAND. LYMPH ND. NEST. LYMPH ND. KIDNEYS ADRENALS SALIVARY GLAND URIN. BLADDER STOMACH DUODENUM PANCREAS JEJUNUM ILEUM COLON ANUS TESTES/OVARIES SEM. VES./UTERUS PROSTATE/VAGINA SKIN MUSCLE NERVE MAMMARY GLAND PITUITARY BRAIN <input checked="" type="checkbox"/> AORTA <input checked="" type="checkbox"/> PULMONARY TRUNK	
<i>Gary B. Marit</i> GARY B. MARIT, MAJ, VC, USA Army Medical Research Unit Toxicology Division 30 April 1992						
PRO. ?	TRIM DR. M 9	EMB 9PP	R.O.	H.T. SLW		
SIGNATURE <i>Jerry Nichols</i>			DATE 21 Apr 92			

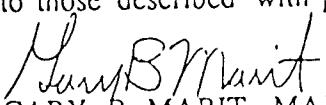
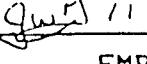
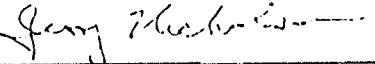
PATHOLOGY CLINICAL RECORD					ACCESSION NO. 622-92	
T.D.NO. 005	ANIMAL NO. 65-4	DATE DIED 10/31/91	DEPT. VS	SEX M	DISP. A	CONDITION G
SPECIES SWINE	STRAIN HAN.	SOURCE NEC. NO. NA		ORIGIN OEVM	INVESTGATOR DR. COOPER	
AGENT NA	CONCENTRATION CONTROL		EUTHANASIA ?	NEC. DATE 10/31/91	TIME DIED NA	
GENERAL CONDITION GOOD, FAIR, POOR, THIN, EMAC., OTHER,				X FOR TISSUE TAKEN		X FOR EXAM MICRO.
CONTROL ANIMAL ON PPB STUDY Histopathologic examination revealed essentially normal tissue.				<input checked="" type="checkbox"/> NASAL SECTION <input checked="" type="checkbox"/> BONE <input checked="" type="checkbox"/> BONE MARROW <input checked="" type="checkbox"/> TRACHEA <input checked="" type="checkbox"/> LARYNX <input checked="" type="checkbox"/> ESOPHAGUS <input checked="" type="checkbox"/> THYROID <input checked="" type="checkbox"/> PARATHYROIDS <input checked="" type="checkbox"/> LUNGS <input checked="" type="checkbox"/> HEART <input checked="" type="checkbox"/> LIVER <input checked="" type="checkbox"/> GALLBLADDER <input checked="" type="checkbox"/> SPLEEN <input checked="" type="checkbox"/> THYMUS <input checked="" type="checkbox"/> MAND. LYMPH ND. <input checked="" type="checkbox"/> MEST. LYMPH ND. <input checked="" type="checkbox"/> KIDNEYS <input checked="" type="checkbox"/> ADRENALS <input checked="" type="checkbox"/> SALIVARY GLAND <input checked="" type="checkbox"/> URIN. BLADDER <input checked="" type="checkbox"/> STOMACH <input checked="" type="checkbox"/> DUODENUM <input checked="" type="checkbox"/> PANCREAS <input checked="" type="checkbox"/> JEJUNUM <input checked="" type="checkbox"/> ILEUM <input checked="" type="checkbox"/> COLON <input checked="" type="checkbox"/> ANUS <input checked="" type="checkbox"/> TESTES/OVARIES <input checked="" type="checkbox"/> SEM. VES./UTERUS <input checked="" type="checkbox"/> PROSTATE/VAGINA <input checked="" type="checkbox"/> SKIN <input checked="" type="checkbox"/> MUSCLE <input checked="" type="checkbox"/> NERVE <input checked="" type="checkbox"/> MAMMARY GLAND <input checked="" type="checkbox"/> PITUITARY <input checked="" type="checkbox"/> BRAIN <input checked="" type="checkbox"/> AORTA <input checked="" type="checkbox"/> PULMONARY TRUNK		
 GARY B. MARIT, MAJ, VC, USA Army Medical Research Unit Toxicology Division						
30 April 1992						
PRO. ?	TRIM DR.M 9	EMB 9 pp	R.O.	H.T. SLW		
SIGNATURE 				DATE 31/04/92		

PATHOLOGY CLINICAL RECORD					ACCESSION NO. 450-92		
T.D. NO. 005	ANIMAL NO. 152-5	DATE DIED NA	DEPT. THV	SEX M	DISP. A	CONDITION G	
SPECIES PIG	STRAIN NA	SOURCE NEC. NO. NA		ORIGIN AF		INVESTGATOR COOPER	
AGENT NA	CONCENTRATION NA		EUTHANASIA PENTABARB		NEC. DATE 18MAR92	TIME DIED NA	
GENERAL CONDITION GOOD, FAIR, POOR, THIN, EMAC., OTHER,						X FOR TISSUE TAKEN X FOR EXAM MICRO.	
<p>GROSS EXAMINATION</p> <p>This pig is in excellent physical and nutritional condition. The only observed lesion is a nodular swelling approximately 7 cm in diameter on the medial aspect of the right thigh. This is the sight of a study related surgical procedure approximately 10 days prior to necropsy. Animal weights and organ weights and measurements are on a separate attached sheet. Organ weights were rounded to the nearest tenth of a gram.</p> <p>HISTOPATHOLOGIC EXAMINATION</p> <ol style="list-style-type: none"> 1. Myocardium; right ventricular free wall: Fibrosis, multifocal, mild. 2. Proximal pulmonary trunk: Fibrosis, focal, moderate. 3. Lung: Lymphoid aggregates, multifocal, minimal to mild. 4. Lung: Fibrosis, interstitial, multifocal, minimal. <p>COMMENT:</p> <p>The most significant finding is focal subendothelial fibrosis in the pulmonary trunk as it leaves the heart. There is within the mid-myocardium of the right ventricle multifocal fibrosis.</p> <p style="text-align: right;"><i>g.w.y 11</i></p>							
PRO. GM/PP/JN	TRIM <i>g.w.y 11</i>	EMB <i>g.w.y 17</i>	R.O.	H.T. SLW			
SIGNATURE <i>George McWhorter</i>			DATE 24 MAR 92				

The pulmonary fibrosis is subjectively more pronounced in this animal than any other pig. However, the difference is minimal and it may be within normal limits. The pulmonary lymphoid aggregates are slightly larger, but much more common than observed in the control.

Gary B. Marit

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Army Medical Research Unit
Toxicology Division
3 April 1992

PATHOLOGY CLINICAL RECORD					ACCESSION NO. 451-92	
T.D.NO. 005	ANIMAL NO. 159-5	DATE DIED NA	DEPT. THV	SEX M	DISP. A	CONDITION G
SPECIES PIG	STRAIN NA	SOURCE NEC. NO. NA	ORIGIN AF	INVESTGATOR COOPER		
AGENT NA	CONCENTRATION NA	EUTHANASIA PENTABARB		NEC. DATE 18MAR92	TIME DIED NA	
GENERAL CONDITION GOOD, FAIR, POOR, THIN, EMAC., OTHER,				X FOR TISSUE TAKEN		X FOR EXAM MICRO.
GROSS EXAMINATION This pig is in excellent physical and nutritional condition. The only observed lesion is multifocal minimal subendocardial hemorrhage; this lesion is believed to be attributed to perfusion. In addition, this animal had a surgical sight similar to pig #450. Animal weights and organ weights and measurements are on a separate attached sheet. Organ weights were rounded to the nearest tenth of a gram.						NASAL SECTION BONE BONE MARROW TRACHEA LARYNX ESOPHAGUS THYROID PARATHYROIDS LUNGS HEART LIVER GALLBLADDER SPLEEN THYMUS MAND. LYMPH ND. MEST. LYMPH ND. KIDNEYS ADRENALS SALIVARY GLAND URIN. BLADDER STOMACH DUODENUM PANCREAS JEJUNUM ILEUM COLON ANUS TESTES/OVARIES SEM. VES./UTERUS PROSTATE/VAGINA SKIN MUSCLE NERVE MAMMARY GLAND PITUITARY BRAIN EYES
HISTOPATHOLOGIC EXAMINATION 1. Heart: Subendocardial fibrosis, diffuse, mild to moderate. 2. Proximal pulmonary trunk: Fibrosis, multifocal, moderate. 3. Lung: Lymphoid aggregates, multifocal, minimal to mild.						
COMMENT: The subendocardial fibrosis tends to be limited primarily to the right ventricle. The thickness is greater than the control pig and the fibrosis does not extend into the underlying myocardium. The lung and pulmonary trunk lesions are similar to those described with pig 450-92.						
 GARY B. MARIT, MAJ, VC, USA Army Medical Research Unit Toxicology Division						
3 April 1992						
 PRO. GM/PP/JN GM TRIM QWY 17 EMB QWY 17 R.O. H.T. GAN 11/2R 92						
SIGNATURE  DATE 3-1-92						

PATHOLOGY CLINICAL RECORD					ACCESSION NO. 452-92	
T.D.NO. 005	ANIMAL NO. 153-8	DATE DIED NA	DEPT. THV	SEX M	DISP. A	CONDITION G
SPECIES PIG	STRAIN NA	SOURCE NEC. NO. NA		ORIGIN AF		INVESTGATOR COOPER
AGENT NA	CONCENTRATION NA		EUTHANASIA PENTABARB		NEC. DATE 18MAR92	TIME DIED NA
GENERAL CONDITION GOOD, FAIR, POOR, THIN, EMAC., OTHER,				X FOR TISSUE TAKEN		X FOR EXAM MICRO.
				NASAL SECTION <input checked="" type="checkbox"/> BONE <input checked="" type="checkbox"/> BONE MARROW <input checked="" type="checkbox"/> TRACHEA <input checked="" type="checkbox"/> LARYNX <input checked="" type="checkbox"/> ESOPHAGUS <input checked="" type="checkbox"/> THYROID <input checked="" type="checkbox"/> PARATHYROIDS <input checked="" type="checkbox"/> LUNGS <input checked="" type="checkbox"/> HEART <input checked="" type="checkbox"/> LIVER <input checked="" type="checkbox"/> GALLBLADDER <input checked="" type="checkbox"/> SPLEEN <input checked="" type="checkbox"/> THYMUS <input checked="" type="checkbox"/> MAND. LYMPH ND. <input checked="" type="checkbox"/> MEST. LYMPH ND. <input checked="" type="checkbox"/> KIDNEYS <input checked="" type="checkbox"/> ADRENALS <input checked="" type="checkbox"/> SALIVARY GLAND <input checked="" type="checkbox"/> URIN. BLADDER <input checked="" type="checkbox"/> STOMACH <input checked="" type="checkbox"/> DUODENUM <input checked="" type="checkbox"/> PANCREAS <input checked="" type="checkbox"/> JEJUNUM <input checked="" type="checkbox"/> ILEUM <input checked="" type="checkbox"/> COLON <input checked="" type="checkbox"/> ANUS <input checked="" type="checkbox"/> TESTES/OVARIES <input checked="" type="checkbox"/> SEM. VES./UTERUS <input checked="" type="checkbox"/> PROSTATE/VAGINA <input checked="" type="checkbox"/> SKIN <input checked="" type="checkbox"/> MUSCLE <input checked="" type="checkbox"/> NERVE <input checked="" type="checkbox"/> MAMMARY GLAND <input checked="" type="checkbox"/> PITUITARY <input checked="" type="checkbox"/> BRAIN <input checked="" type="checkbox"/> EYES		
GROSS EXAMINATION <p>This pig is in excellent physical and nutritional condition. The only observed lesion is a nodular swelling approximately 7 cm in diameter on the medial aspect of the right thigh. This is the sight of a study related surgical procedure approximately 10 days prior to necropsy. Animal weights and organ weights and measurements are on a separate attached sheet. Organ weights were rounded to the nearest tenth of a gram.</p> <p>During tissue trimming on 26 March a 0.5x0.2cm yellow gritty nodule was observed on the ventral edge of the right medial lung lobe.</p>				HISTOPATHOLOGIC EXAMINATION <ol style="list-style-type: none"> 1. Distal aorta: Mineralization, multifocal, mild. 2. Lung: Pyogranuloma, focal, moderate. 3. Lung: Lymphoid aggregates, multifocal, minimal to mild. 4. Lung: Fibrosis, multifocal, mild. 5. Proximal pulmonary trunk: Fibrosis, focal, segmental, mild. 		
PRO. GM/PP/JN	GM TRIM 3/26/92	EMB 3/26/92	R.O.	H.T.GHN 11 Mar 92		
SIGNATURE George Richardson			DATE	3/26/92		

COMMENT:

In contrast to the fibrosis of the pulmonary trunk previously observed, it is a circumferential subendothelial change rather than extending into the tunica media. The cause of the aortic mineralization and the pulmonary pyogranuloma are not known. The pulmonary fibrosis coded above was in the same section of lung as the granuloma and is likely a related lesion.



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Army Medical Research Unit
Toxicology Division

3 April 1992

PATHOLOGY CLINICAL RECORD					ACCESSION NO. 453-92	
T.D.NO. 005	ANIMAL NO. 13-7	DATE DIED NA	DEPT. THV	SEX M	DISP. A	CONDITION G
SPECIES PIG	STRAIN NA	SOURCE NEC. NO. NA	ORIGIN AF	INVESTGATOR COOPER		
AGENT NA	CONCENTRATION NA	EUTHANASIA PENTABARB	NEC. DATE 18MAR92	TIME DIED NA		
GENERAL CONDITION GOOD, FAIR, POOR, THIN, EMAC., OTHER,				X FOR TISSUE TAKEN		X FOR EXAM MICRO.
				NASAL SECTION BONE BONE MARROW TRACHEA LARYNX ESOPHAGUS THYROID PARATHYROIDS X LUNGS X HEART X LIVER X GALLBLADDER X SPLEEN THYMUS MAND. LYMPH ND. MEST. LYMPH ND. X KIDNEYS X ADRENALS SALIVARY GLAND URIN. BLADDER STOMACH DUODENUM PANCREAS JEJUNUM ILEUM COLON ANUS TESTES/OVARIES SEM. VES./UTERUS PROSTATE/VAGINA SKIN MUSCLE NERVE MAMMARY GLAND PITUITARY X BRAIN X EYES		
GROSS EXAMINATION <p>This pig is in excellent physical and nutritional condition. The only observed lesions are multifocal minimal subendocardial hemorrhage and multifocal minimal epicardial hemorrhage; each lesion is believed to be attributed to perfusion. In addition, this animal had a surgical sight similar to the other treated pigs. Animal weights and organ weights and measurements are on a separate attached sheet. Organ weights were rounded to the nearest tenth of a gram.</p>						
HISTOPATHOLOGIC EXAMINATION <ol style="list-style-type: none"> 1. Proximal pulmonary trunk: Fibrosis, multifocal, segmental, minimal. 2. Heart, right ventricle: Hemorrhage and edema, focally extensive, moderate. 3. Heart, left ventricle: Fibrosis, focal, minimal. 4. Lung: Lymphoid aggregates, multifocal, minimal to mild. 						
PRO. GM/PP/JN	GM TRIM QW 17	EMB QW 17	R.O.	H.T. GHAN 1 APR 92		
SIGNATURE <i>Jerry Richardson</i>			DATE <i>24 Mar 92</i>			

COMMENT:

The pulmonary artery fibrosis is similar to but less severe than that seen in animal 452-92. The hemorrhage and edema observed in the heart corresponds to one of the grossly observed lesions and is likely attributed to perfusion.

Gary B. Marit
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Army Medical Research Unit
Toxicology Division

3 April 1992

Pathologist Report APPENDIX C.

AN INQUIRY INTO THE CHRONIC EFFECTS OF POSITIVE PRESSURE BREATHING NARRATIVE PATHOLOGY REPORT

GROSS OBSERVATIONS:

At necropsy all pigs utilized in this study were in good general condition. Subendocardial hemorrhage was observed in the control and two test animals; one test pig also had subepicardial hemorrhage. One animal had a small nodule in the lung. Animal and organ weights, organ measurements, and complete gross observations are included in the individual animal's Pathology Clinical Record. Statistical analysis revealed a significant difference in the increased weight of the left atrium in the test pigs versus the control. The statistical worksheet is attached.

HISTOPATHOLOGY:

The histopathologic diagnosis for each tissue alteration and comment is included in the individual animal's Pathology Clinical Record and an Addendum Narrative Report. Analysis of the findings failed to disclose any significant differences between the control and test pigs. The hemorrhages in the heart are attributed to perfusion. The pulmonary nodule observed in pig 452-92 is a pyogranuloma and is most likely in response to aspirated foreign material.

DISCUSSION:

Gross and histologic examination of the left atrial myocardium and gross examination of the mitral valve failed to explain the increased left atrial weight in the test pigs. Because of the small number of pigs utilized in this study it is possible that the variation in the atrial weights may be within the normal range. If the difference is real a functional deficit in the mitral valve is a possible explanation. Perhaps the echocardiographic data collected could resolve this question.

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30 April 1992

ADDENDUM PATHOLOGY REPORT (#s 448-92 and 450-92 to 453-92)

Histopathologic examination of additional sections of the pulmonary trunk (and aorta) from the control pig (448-92) revealed circumferential and multifocal dense fibrosis similar to the other pigs on the study. These areas of fibrosis occurred at or near the pulmonic valve and are believed to be a normal morphologic finding.

Most of the additional sections of aorta and pulmonary arteries from the test pigs (450-92 to 453-92) were essentially normal. There was usually one section that demonstrated fibrosis similar to that seen in the original sections; however, each was believed to have been taken from essentially the same area (near the pulmonic valve). The mineralization of the distal aorta observed in pig 452-92 was not seen in subsequent recut sections.

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